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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,652	08/14/2001	Kevin Burgess	17575.0661	7332

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EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,652	BURGESS ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-58* is/are pending in the application.

4a) Of the above claim(s) *13-19,30-32,37-39 and 44-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-29,33-36 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/2002* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election of anthracene chromophore in claim 21, BODIPY emitter in claim 23, succinimidyl ester group in claims 25, 26, 42, and 43, nucleic acid in claims 27-29 and 34-36 on December 30, 2002 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Since the examiner agreed to combine Groups II and III (claims 20-43) in previous office action, based on applicant's species election, claims 20-29, 33-36, and 40-43 will be examine in this office action.

Priority

2. The examiner notes that applicant claimed priority for U.S. Patent Application Serial No. 09/430,718 in preliminary amendment filed on June 13, 2001. However, corrected Application No. should be 09/460,718 and is not 09/430,718. Applicant is also required to update the status of case 09/460, 718 since this case has been patented.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be

incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 20-29, 33-36, and 40-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification provides an adequate written description for two fluorescence dyes, A and B (see the specification, page 15) wherein, in fluorescence dye A, anthracene is a UV absorbing chromophore and BODIPY is a fluorescence emitter. The specification also (see page 15, last paragraph) describes that perylene, anthracene, tetracene, fluorescein, and BODIPY can

be used as a fluorescence absorbing chromophore while fluorescein, rhodamine, BODIPY, squareine and a cyanine dye can be used as emitters. However, the specification fails to adequately describe: (1) synthesis of a fluorescence dye comprising any kind of UV absorbing chromophore and any kind of fluorescence emitter as recited in claim 20; (2) a fluorescence dye comprising any kind of anthracene derivative and any kind of BODIPY fragment wherein the anthracene derivative and the BODIPY fragment can be connected by any possible way as recite in claim 33; and (3)a fluorescence dye comprising any kind of anthracene derivative, any kind of BODIPY fragment, and a chromophore wherein the anthracene derivative and the BODIPY fragment can be connected by any possible way and wherein the chromophore and the anthracene derivative can absorb in mutually exclusion regions of the UV spectrum. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics*, Inc., 48 USPQ2d 1641, 1646 (1998).

In this instant case, a fluorescence dye in claims 20 was read as a fluorescence dye comprising any kind of UV absorbing chromophore and any kind of fluorescence emitter. Claim 21 was read as a fluorescence dye comprising a UV absorbing chromophore and a fluorescence emitter wherein the chromophore was selected from perylene, anthracene, tetracene, fluorescein,

and BIDIPY. Claim 23 was read as a fluorescence dye comprising a UV absorbing chromophore and a fluorescence emitter wherein the emitter was selected from fluorescein, rhodamine, BODIPY, squareine and a cyanine dye. Although the specification adequately describes two fluorescence dyes A and B (see the specification, page 15) wherein anthracene is as a UV absorbing chromophore and BODIPY is as a fluorescence emitter, the specification fails to adequately describe how to synthesize a fluorescence dye comprising any kind of UV absorbing chromophore and any kind of fluorescence emitter as recited in claims 20. For example, the specification does not describe to synthesize a fluorescence dye comprising a UV absorbing chromophore and a fluorescence emitter wherein perylene is a UV absorbing chromophore and squareine is a fluorescence emitter. In view of the specification, It is unclear whether this fluorescence dye can be synthesized. Furthermore, the specification fails to describe how to synthesize a fluorescence dye comprising any kind of anthracene derivative and any kind of BODIPY fragment wherein the anthracene derivative and the BODIPY fragment can be connected by any possible way as recite in claim 33 and a fluorescence dye comprising any kind of anthracene derivative, any kind of BODIPY fragment, and a chromophore wherein the anthracene derivative and the BODIPY fragment can be connected by any possible way and wherein the chromophore and the anthracene derivative can absorb in mutually exclusion regions of the UV spectrum as recited in claim 40. In view of the specification, it is unclear whether these fluorescence dyes can be synthesized. Therefore, claims 20-29, 33-36, and 40-43 encompass numerous unknown and unidentified fluorescence dyes that miss from the disclosure and the

general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

With limited disclosure provided by the specification, the skilled artisan cannot envision all possible fluorescence dyes recited in claims 20-29 and 33 and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co.* Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481, 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 20, 21, and 23-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee *et al.,* (Nucleic Acids Research, 25, 2816-2822, July 1997).

Regarding claims 20, 21, and 23-28, claim 20 requires to label a biomolecule (ie., nucleic acid) by contacting a biomolecule with a fluorescent dye comprising a UV absorbing chromophore and a fluorescent emitter wherein the chromophore and fluorescent emitter are conjugated to each other such that energy transfer between the chromophore and the fluorescent emitter through bond mechanism and wherein the UV chromophore absorbs energy at a lower wavelength than that emitted by the fluorescent emitter. Claim 21 requires that the chromophore is a fluorescein. Claim 23 requires that the emitter is a rhodamine. Claim 24 requires that the dye has a functional group suitable for covalently attached the dye to the biomolecule. Claims 25 and 26 require that the dye has a succinimidyl ester group. Claims 27 and 28 require that the biomolecule is a nucleic acid such as DNA.

Lee *et al.,* teach four new energy transfer dyes for DNA sequencing. As shown in Figure 5, these new dyes were formed by connecting a donor dye group and an acceptor dye group. In four energy transfer dyes, the donor dye groups were 5- or 6-carboxy isomer of 4'-aminomethylfluorescein and the acceptor dye groups were a novel set of four 4,7-dichloro-substituted rhodamine dyes (see abstract in page 2816 and Figure 5). These new dyes was used to label an oligonucleotide primer for DNA sequencing by reaction of succinimidyl esters of the dyes with 5' aminohexyl-derivatized universal primer (see page 2818, left column, third and fourth paragraphs) as recited in claim 20. First, since it is known that UV wavelength is around 80-800 nm, donor dye groups (ie., 5- or 6-carboxy isomers of 4'-aminomethylfluorescein) and acceptor

dye groups (ie., 4,7-dichloro-substituted rhodamine dyes) are UV absorbing chromophores and fluorescent emitters respectively as recited in claim 20 because the absorbance and emission wavelengths of fluorescein dye and rhodamine dye are in UV range (for emission spectra of fluorescein dye and rhodamine dye, see Figures 3-5 in this reference). According to the specification, fluorescence energy transfer "through bond mechanism" is finished by covalent bonds between a donor dye group and an acceptor dye group in a fluorescence dye (see the specification, Figure 1 B and pages 13 and 14). Because these new dyes taught by Lee *et al.,* are connected by a donor dye group and an acceptor dye group (see Figure 5), these new dyes transfer fluorescence energy by a bond mechanism. Because it is known that absorbance wavelength of a fluorescence dye must be lower than its emission wavelength, UV chromophore absorbs energy at a lower wavelength than that emitted by the fluorescent emitter as recited in claim 20. For above reasons, claim 20 is anticipated by Lee *et al.*. Second, because these new dyes taught by Lee *et al.,* are connected by a fluorescence derivative (ie., donor dye group) and a rhodamine derivative (ie., an acceptor dye group) (see Figure 5), claims 21 and 23 are anticipated by Lee *et al.*. Third, because these new dyes was used to label an oligonucleotide primer for DNA sequencing (see page 2818, left column, third and fourth paragraph), claims 27 and 28 are anticipated by Lee et al.. Fourth, because the oligonucleotide primer for DNA sequencing is labeled by a reaction of succinimidyl esters of the dyes with 5' aminohexyl-derivatized universal primer (see page 2818, left column, third paragraph), succinimidyl esters are functional groups suitable for covalently attached the dye to the biomolecule (ie., oligonucleotide) as recited in claims 24-26.

Therefore, Lee *et al.,* teach all limitations recited in claims 20, 21, 23, 27, and 28.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.,* as applied to claims 20, 21, and 23-28 above, and further in view of Bauman *et al.,* (J Histochem Cytochem., 29,227-37, 1981).

The teachings of Lee *et al.,* have been summarized previously, *supra.*

Lee *et al.,* do not disclose to prepare a RNA labeled with a fluorescence dye as recited in claim 29.

Bauman *et al.,* do teach a RNA labeled with a fluorescence dye (ie., rhodamine or fluorescein) (see left column in page 229 and right column in page 230).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have labeled a RNA with a fluorescence dye as recited in claim 29 in view of the prior art of Lee *et al.,* and Bauman *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Lee *et al.,* because Bauman *et al.,* taught successfully to label a RNA with a fluorescence dye and the simple replacement of one nucleic acid with well known properties (ie. DNA) from another nucleic acid with well known properties (ie., RNA) during the process for using fluorescence dyes prepared by Lee *et al.,* would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

10. Claims 33-35 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kollmannsberger *et al.,* (Angew. Chem. Int. Ed. Engl. 36, 1333-1335, 1997) in view of Lee *et al.,* (July 1997).

Kollmannsberger *et al.,* teach electrogenerated chemiluminescence and proton-dependent switching of fluorescence. Synthesized compounds 1, 2a-2c, and 4a and 4b were BODIPY fragments wherein R could be Me, H or Co2Et (page 1333, right column). Compound 3 contained an anthracene derivative (top) and a BODIPY fragment (bottom) that had different emission wavelength from that of the compounds 1, 2a-2c, and 4a and 4b (page 1333, right column and Table 1). Because the anthracene derivative and the BODIPY fragment in compound 3 were conjugated to each other (see page 1333. left column), the compound 3 and fluorescence dye as recited in claim 33 have identical structures.

Kollmannsberger *et al.,* do not disclose to covalent bond a fluorescence dye to a biomolecule (ie., DNA) as recited in claims 33-35 and 41.

Lee *et al.,* do teach to covalent bond a fluorescence dye to a biomolecule (ie., DNA) (see page 2818, left column).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to have labeled a biomolecule (ie., DNA) with a fluorescence dye as recited in claim 33 wherein the dye was covalently bonded to the biomolecule in view of the prior art of Kollmannsberger *et al.,* and Lee *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Lee *et al.,* because the simple replacement of one fluorescence dye with well known properties (ie., a dye taught by Lee *et al.,*) from another

fluorescence dye with well known properties (ie., the compound taught by Kollmannsberger *et al.,*) during the process of labeling a biomolecule (ie., DNA) with a fluorescence dye would have been, in the absence of an unexpected result, prima facie obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

11. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kollmannsberger *et al.,* in view of Lee *et al.,* as applied to claims 33-35 and 41 above, and further in view of Bauman *et al.,* (J Histochem Cytochem., 29,227-37, 1981).

The teachings of Kollmannsberger *et al.,* and Lee *et al.,* have been summarized previously, *supra.*

Kollmannsberger *et al.,* and Lee *et al.,* do not disclose to prepare a RNA labeled with a fluorescence dye as recited in claim 36. .

Bauman *et al.,* do teach a RNA labeled with a fluorescence dye (ie., rhodamine or fluorescein) (see left column in page 229 and right column in page 230). .

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have labeled a RNA with a fluorescence dye as recited in claim 29 in view of the prior art of Kollmannsberger *et al.,* Lee *et al.,* and Bauman *et al.*. One having ordinary skill in the art would have been motivated to do so because Bauman *et al.,* taught successfully to label a RNA with a fluorescence dye and the simple replacement of one nucleic acid with well known properties (ie. DNA) from another nucleic acid with well known properties (ie., RNA) during the process for using fluorescence dyes prepared by Kollmannsberger *et al.,* would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

12. No claim is allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
March 10, 2003

Ethan Whisenant, Ph.D.
Primary Examiner
Art Unit 1634